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DIET, LIFESTYLE AND CHRONIC KIDNEY DISEASE

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Diet, Lifestyle and Chronic Kidney Disease

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To my family

ABSTRACT

Chronic kidney disease (CKD) is a rapidly growing global health problem, affecting 5-10% of the general population, and individuals with CKD have a substantially increased risk of morbi-mortality. Early detection and treatment can delay or prevent onset many of the adverse outcomes of CKD. However, due to insufficient knowledge about factors that drive CKD incidence, renal function decline and complications of CKD, our capacity to implement effective preventive strategies is limited. This thesis explores associations of dietary/lifestyle risk factors with kidney dysfunction and diet-related outcomes.

Study I investigated the associations between dietary fiber and systemic inflammation, kidney function and mortality risk. We found that higher dietary fiber intake was associated with better renal function and lower inflammation. Higher fiber intake was also associated with better survival, especially in individuals with manifest CKD.

Study II investigated the implications of circulating phosphate levels, reflecting in part dietary intake of phosphorus, on the risk of adverse clinical outcomes in patients with manifest cardiovascular disease (CVD). We found that both higher and lower phosphate levels associated with increased risk of adverse outcomes during the index CVD hospitalization and within one-year post-discharge. Risk associations were already present in the normal-range serum phosphate levels.

Study III addressed the pro-inflammatory load of the diet as a potential cause of kidney dysfunction. By combining putatively pro-inflammatory and anti-inflammatory effects of nutrients, vitamins, and trace elements, a dietary pattern was generated that correlated with both renal function and systemic inflammatory biomarkers. We found that pro-inflammatory diet associated with lower kidney function and that the association between this dietary pattern and renal function was substantially mediated by systemic inflammation.

Study IV addressed the association between dietary acid load and mortality in the community. Both excessive dietary alkalinity and acidity, showed weak associations with mortality in a U-shaped fashion. An acid-base balanced diet was associated with the minimum mortality rate. However, the magnitude of mortality reduction was modest, suggesting that dietary modifications of the alkalinity of the diet may not be very relevant overall to reduce mortality risk.

Study V investigated whether the association between obesity and incident CKD affected by genetic confounding and/or explained by obesity-associated diabetes among twins**.** We observed that controlling for shared risk factors between twin pairs minimally affected the association between body mass index (BMI) and CKD. In twins with discordant BMI, heavier siblings had a higher adjusted incidence rate of CKD than leaner ones. After adjusting for diabetes development, the strength of the association was reduced (suggesting effect mediation), but remained statistically and clinically significant. We concluded that a higher BMI, irrespective of genetic confounding or incident diabetes, was associated with CKD.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers. They are referred to in the text by their Roman numerals (I-V):

I. **Xu H,** Huang X, Risérus U, Krishnamurthy VM, Cederholm T, Arnlöv J, Lindholm B, Sjögren P, Carrero JJ. Dietary fiber, kidney function, inflammation, and mortality risk. Clinical journal of the American Society of Nephrology 2014 9;12 2104-10

II. **Xu H,** Evans M, Gasparini A, Szummer K, Spaak J, Ärnlöv J, Lindholm B, Jernberg T, Carrero JJ. Outcomes associated to serum phosphate levels in patients with suspected acute coronary syndrome. International journal of cardiology 2017 245; 20-26

III. **Xu H,** Sjögren P, Ärnlöv J, Banerjee T, Cederholm T, Risérus U, Lindholm B, Lind L, Carrero JJ. A pro-inflammatory diet is associated with systemic inflammation and reduced kidney function in elderly adults. Journal of nutrition 2015 145;4 729-35

IV. **Xu H,** Åkesson A, Orsini N, Hakansson N, Wolk A, Carrero JJ. Modest U-Shaped Association between Dietary Acid Load and Risk of All-Cause and Cardiovascular Mortality in Adults. Journal of nutrition 2016 146;8 1580-5

V. **Xu H**, Kuja-Halkola R, Chen X, Magnusson P, Svensson P, Carrero JJ. Impact of genetic confounding and incident diabetes in the association between body mass index and chronic kidney disease: a population-based swedish twin study. In submission.

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Not included in this thesis

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LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
ADII	Adapted Dietary Inflammatory Index
BMI	Body Mass Index
CKD	Chronic Kidney Disease
COSM	Cohort of Swedish Men
CRP	C-Reactive Protein
CVD	Cardiovascular disease
ESRD	End-Stage Renal Disease
eGFR	Estimated glomerular filtration Rate
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors
SALT	Screening Across Lifespan Twin study
SCREAM	Stockholm CREAtinine Measurements project
SMC	Swedish Mammography Cohort
STR	Swedish Twin Registry
ULSAM	Uppsala Longitudinal Study of Adult Men

1. BACKGROUND

1.1 INTRODUCTION

Chronic kidney disease (CKD), defined as albuminuria and/or decreased glomerular filtration rate (GFR) [1], is a rapidly growing global health problem, affecting about 10% of the community, with a much higher prevalence among the older and those with comorbid diabetes or cardiovascular disease (CVD) [2]. Renal failure or end-stage renal disease (ESRD) represents the end of disease progression, requiring renal replacement therapy in the form of dialysis or renal transplantation. CKD patients, even at early disease stage, have a substantially increased risk of morbidity due to CVD, malnutrition, inflammation, mental disorders, and other complications, which collectively leads to high hospitalization rates and excess mortality risk [3, 4]. Adverse outcomes of CKD can be prevented by early detection. However, due to insufficient knowledge about factors that drive renal function decline, CKD and ESRD incidence, our capacity to implement preventive strategies is limited.

A few management options are able to retard CKD progression and reduced CKD-related complications, some of them including dietary modifications [5]. Diet restriction has been a cornerstone management strategies in patients with CKD for more than one century, such as the use of low protein diets for secondary CKD prevention [6, 7]. However, many dietary aspects remained unexplored in their potential to alleviate CKD outcomes. It is true that current guidelines for CKD management recommend a number of dietary changes [5, 8], but these derived from observations in population screenings and fail to address important components of the modern diet. Finally, it is acknowledged that adherence to a healthy lifestyle is followed by a reduced risk of worse outcomes in the general population [9], but few studies have evaluated selected lifestyle factors in CKD [10].

1.2 QUANTITY AND QUALITY OF SINGLE NUTRIENTS

The role of diet in health and disease is far more complex than the isolated effects of single nutrient combinations, and public health guidelines for primary prevention of chronic diseases are progressively shifting from a single-nutrient/food item focus to recommendations regarding whole foods and patterns of dietary quality. However, the dietary management of CKD and ESRD patients has focused on limiting the quantity within single nutrient of substances such as protein, phosphorus, potassium, or sodium that can accelerate kidney damage and/or accumulate in uremia reaching toxic levels [5, 8]. Less or no attention has been devoted to the quality and the diversity of the diet, and with these restrictions in mind, it is probably not unexpected that the quality of the diet in patients with CKD is not considered as “healthy” [7, 11-14].

For instance, although much research addresses the safety and effectiveness of low protein diets, little focus has been given to protein sources. Recent cohort studies intriguingly suggest that whereas high intake of animal protein associates with increased progression of CKD, substitution

for plant protein reduces considerable this risk [15], and associates with reduced mortality rates in individuals with CKD [16].

Further, current guidelines fail to make any recommendation regarding the intake and the quality of many other nutrients. This is the case for dietary fat, with observational studies associating saturated fatty acids (SFAs) intake with CKD progression and incident albuminuria [17-20] and even interventional trials and meta-analyses indicating beneficial effects of polyunsaturated fat intake in retarding kidney function decline [21-24]. One recent cohort study showed that a high lipophilic index, which was utilized as a reflection of dietary fat quality, was independently associated with the odds CKD progression [25].

The quality of carbohydrate intake has likely a major influence on risk of many chronic diseases. Consumption of high glycemic load grains, potatoes, or added sugars has been related to the development of non-communicable diseases including cardiovascular disease, diabetes and obesity; On the other hand, whole fruits, legumes, leafy vegetables, and kernel grains appear as protective for these outcomes [26]. For CKD, a number of studies showed that the consumption of artificially sweetened sodas associates with albuminuria incidence and rapid GFR decline [27, 28]. However, with few exceptions this has not translated into interventional studies restricting sugar/sweetener intake in CKD patients. A clinical trial in CKD patients reported that a diet with low amounts of fructose was effective in reducing a number of inflammatory biomarkers and blood pressure compared a control diet with habitual fructose intake [29]. Dietary sugar may increase uric acid levels, promote hyperglycemia, hypertension and obesity, increasing the risk of diabetes mellitus, which is one of the most common causes of CKD [30].

1.2.1 Dietary fiber

A high dietary fiber intake is recommended as a part of healthy diet in many clinical guidelines for the prevention of several chronic diseases. There are numerous meta-analyses showing an inverse association between dietary fiber and CVD event or CVD mortality [31], as well as glycemic control and diabetes management [32], metabolic syndrome [33] and cancer risk reduction [34]. However, because of hyperkalemia fear, fruits and vegetables (the main source of fiber), patients with CKD are often advised under current dietary fiber recommendations [5, 8]. Studies on the benefits or harms of fiber intake on CKD are, so far, limited. Interestingly, a meta-analysis from 14 clinical trials in patients without CKD showed that dietary fiber fortification significantly lowered serum urea and plasma creatinine concentrations in a very short follow up period [35]. Dietary fiber correlated with reduced risk of CVD events and/or mortality in adults with reduced renal function [31, 36]. The possible benefits of increased fiber intake are many, but to date have not been investigated. For instance, outside the renal arena, a study from the Prevención con Dieta Mediterránea (PREDIMED) trial, showed a strong negative correlation between dietary fiber and subsequent risk of death, which was mainly attributed to a lower risk of CVD-deaths [37]. The Third National Health and Nutritional Examination Survey (NHANES III) cohort reported a similar inverse correlation between dietary fiber and inflammation and death, which was stronger in individuals with CKD compared those without [38]. Similarly, **Study I** showed dietary fiber intake positively associated with renal function and negatively associated with inflammation. Higher fiber intake was also associated with lower mortality risk in the community [39].

The cardio-renal protective effect of dietary fiber is plausibly attributed to health benefits of fiber on intermediate risk factors for CVD including blood pressure reduction, decreased waist circumference, body weight loss, lowering fasting blood sugar and high-density-lipoprotein-cholesterol [40]. In addition, dietary fiber may delay gastric emptying, bind bile acid, compete with dietary protein as substrates for fermentation by the gut flora [41]. In this sense, a recent trial in CKD patients showed that increased fiber intake was similarly effective to pharmacological treatments in the management of constipation, a common complication of CKD [42]. Dietary fiber is also accompanied by increased vitamin intake and antioxidant intake, that can lead to lower endogenous production of acid, and reduced production of uremic toxins such as p-cresyl sulfate and indoxyl sulfate, two considered risk factors for accelerated CKD progression [43]. The favorable effect of fiber-rich diets on systemic inflammation is also suggested by a previous epidemiologic study [44].

After our study was published [39], other reports have confirmed and expanded clinical associations of increased fiber intake in persons with CKD: In population-based cohort, higher fiber intake associated with a decreased risk of CKD [45] and in another study lower dietary fiber associated with faster CKD progression in CKD patients [46]. In addition, we could also show that a diet high in protein and poor in fiber increases uremic toxin production [47] and associates with the incidence of CVD events in patients with CKD [48]. High protein and low fiber also lowers the acid load. High dietary acid load was significantly correlated to the risk of ESRD among individuals with albuminuria from NHANES III [49].

1.2.2 Phosphorus

Dietary phosphorus comes from organic and inorganic sources. Organic phosphorus is bound to dietary protein, and therefore variations in the amount of protein intake will primarily affect phosphorus intake. However, the intestinal absorption of dietary phosphorus is higher if coming from animal sources (40-60% absorption) than from vegetable sources (10-30% absorption). On the other hand, inorganic phosphorus, which is often added to processed foods for conservation and enhancement of taste, is almost entirely absorbed in the intestine and represents an important hidden source of phosphorus in the diet. The estimation of phosphorus intake from dietary recalls is challenging, since inorganic phosphorus content is neither reported in food labels nor accounted for in food composition software.

Said this, serum phosphate concentration is affected by many processes that regulate phosphorus metabolism, including excretion of phosphorus by renal tubules, and electrolyte exchanges in bone metabolism. An increase in the serum phosphate concentration over the normal range is frequently a feature at a late stage of CKD, mainly when eGFR<45 ml/min, a state of kidney disease in which compensatory mechanisms are no longer sufficient to maintain phosphorous balance [50]. On maintenance dialysis, hyperphosphatemia risks are particularly heightened, with a prevalence as high as 50% [51].

Current recommendations for phosphorus intake in CKD recommend to reduce intake to 800-1000 mg/day, adding phosphate binders if found appropriate [52]. These recommendations are rooted on the strong adverse event prediction of serum phosphate levels in CKD patients. However, in truth, there are very few studies to support the effect of dietary restriction on CKD outcomes and

results are mixed [53-59]. Although many studies have explored the risks of hyperphosphatemia in CKD, this may not be well-known outside nephrology. **Study II** demonstrated that even in patients with normal renal function, variations in serum phosphate within the normal range were associated with in-hospital and after discharge mortality in acute myocardial infarction patients [60].

1.3 DIETARY PATTERNS

Because of the inherent associations of macro- and micronutrients within foods and patterns of diet, it is likely that the quality of the diet and the cumulative exposure to a specific dietary pattern may be more influential on CKD than excess or deficiency of one specific macro- or micronutrient [61]. The role of the food and regulating homeostasis is far more complicated than delivering a single mix of nutrients, Although, there is some clinical trial evidence supporting the benefit of a holistic diet modification versus single nutrient approaches [62, 63], most of information on healthy-eating patterns derive from observational studies. These recent studies mainly emerge from large population-based studies where serum creatinine is available and estimated GFR can be calculated, bringing new light into primary prevention strategies for CKD.

1.3.1 Healthy dietary patterns

The scientific community has developed a wide array of methods identify dietary patterns and assess their impact on health. The most common approach has been the creation of scores of different foods that indicate the degree of adherence to the healthy dietary patterns and then use the score to examine its association with clinical outcomes. Such as the case of the Healthy Eating Index (HEI), which has been associated with lower risk of albuminuria in participants with diabetes from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) [64]. Substitution analyses from HEI score attributed in part this effect to fruit and vegetable intake; when participants consumed >14 servings/week of fruit and vegetables, their associated ESRD risk lowered by 2-5%, and their mortality risk was 5-10% lower [65].

The characteristics of Mediterranean Diet Score (MDS) generally considers a high intake of olive oil, fresh fruits, vegetables, whole grains, legumes and nuts, a moderate intake of fish and other sea food, a low-to-moderate intake of cheese and yogurt, a low intake of sweets and red meat, finally accompanied by a moderate intake of red wine. Adherence to MDS has been correlated with better renal function in cross-section study [66] and with a slight improvement of renal function after one year of intervention in high risk of elderly patients with coronary heart disease [67]. Following a MDS was also associated with lower risk of incident CKD and slower kidney function decline [68], predicting the risk of mortality among persons with CKD [69].

A low salt diet, represented by adherence to Dietary Approaches to Stop Hypertension (DASH) patterns, correlated with reduced CKD incidence in two population-based cohorts [70, 71] and in selected high-risk populations that may benefit from reduced salt intake, such as individuals with dysglycemia, dyslipidemia or hypertension [72]. Low-moderate salt consumption also appears to potentiate the anti-proteinuric effect of angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) and vitamin D receptors [73, 74]. Said these, DASH-style dietary interventions have yet been conducted to discern its benefits in patients with CKD.

The NIH-AARP Diet and Health Study showed collectively that these dietary quality scores (Alternate HEI, HEI, MDS, and DASH) were associated with 15-30% decreased risk of the composite outcome of dialysis and renal death [75]. The common characteristics of these scores of healthy eating were summarized in recent meta-analyses and include generally increased intake of fruits and vegetables, but reduced intake of red meat, refined sugar and sodium, features that were consistently associated with decreased mortality risk in people with CKD [76]. Nonetheless, the association between healthy dietary patterns and risk of ESRD did not attain statistical significance [76]. The consequences of healthy eating in dialysis populations have been scarcely studied, with to date only one recent multinational cohort study providing some light in this issue. The results so far are disappointing, as no association was observed between adherence to MDS or DASH diets and the risk of (cardiovascular) mortality [77]. It may be that dialysis patients are too sick, and dietary modifications may not be enough. We could also consider that dialysis patients are a selected group of survivors of CKD progression. In any case, we need dietary intervention studies to find this out. Currently, interventional evidence on the effects of dietary changes beyond protein intake in adults with CKD are very preliminary, affected by low samples size and short duration, not having examined mortality as an endpoint [78-80].

1.3.2 Unhealthy dietary patterns

Western diets are characterized by a high intake of red meat, processed foods, butter, high-fat dairy products, sweets, and a low intake of fruits, vegetables, highly refined grains and sugars. Adherence to a Western diet has been related to increased risk of albuminuria and more faster kidney function decline [81].

The components of the diet affect the acid-base balance of the human body [82, 83]. Net alkaline foods generally include fruits and vegetables, and net acidified foods include meat, cheese, grains and eggs [84]. While the so-called Western diets are collectively acidifying diets, vegetarian diets are considered to be alkalizing [85, 86]. Excess of acidifying over alkalinizing nutrients may in theory lead to endogenous acid production and potentially metabolic acidosis [87]. Dietary acid load can estimated by validated algorithms that precisely consider this acid- or base-forming capacity of nutrients [88, 89]. **Study IV** studied these estimations of acid load in a large community screening, and results suggested that both dietary acid and alkali excess may entail a similarly increased mortality risk, especially due to CVD-related causes [90].

Diet most likely plays a crucial role in the regulation of systemic inflammation [91]. Nutrients considered anti-inflammatory, such as n-3 polyunsaturated fatty acids (PUFA), fiber, or vitamins [92-94], related to lower risk of albuminuria, and less rapid kidney function decline [39, 95, 96]. On the other hand, nutrients with pro-inflammatory properties, such as SFAs, or sugars [97, 98] associated with declined renal function [99, 100]. The overall balance in the intakes of pro- and anti-inflammatory food items/nutrients may impact on inflammatory status. Using validated scores [101, 102] of the pro-inflammatory net effect of diets, **Study III** convincingly showed that such unhealthy pattern correlates with both renal function and systemic inflammatory biomarkers [103].

1.4 LIFE STYLE FACTORS AND CKD

Unhealthy diet, obesity [104], physical inactivity, smoking, alcohol consuming, drug abuse [105], sleep loss or shift work, stress [106], and overuse of technologies such as mobile telephone and computer [107] are modern examples of unhealthy lifestyles. It is recognized that following a healthy lifestyle is correlated with better outcomes in the general population [108]. Unhealthy lifestyles are leading causes of morbidity including obesity, diabetes, CVD, musculoskeletal disease, dementia, cancer and mortality worldwide [105, 108]. Smoking, poor dietary quality, low physical activity, and excess alcohol intake account for over 30% of deaths in the U.S. [105].

1.4.1 BMI

While some population-based studies report an association between obesity and incident CKD, evidence somewhat conflicting [109-113]. Several explanations for these discrepancies have been suggested, including selection bias, insufficient control of confounders, or problems with normalization to body surface area in estimated glomerular filtration rate equations [109, 112]. Since both obesity [114] and CKD [115] are partly inherited, genetic factors shared by obesity and CKD could as well explain this association. Despite a number of metabolic factors have been thought as contributors to obesity-induced CKD, the underlying signaling mechanisms are not well understood [116]; It could be that obesity leads to CKD by prompting the development of other intermediate diseases such as diabetes [117]. In **Study V**, we observed, however, that neither genetic confounding nor incident diabetes abrogated the association between a high-body mass index (BMI) and CKD risk, providing strong evidence in support of a direct effect.

1.4.2 Other lifestyle risk factors

Scarce number of studies have evaluated lifestyle habits in CKD populations. Perhaps not unexpectedly, they generally report adverse outcomes associated with smoking and physical inactivity [10, 118]. Counter-intuitively though, studies that test the correlation between alcohol consumption with the risk of CKD observed mostly inverse associations, and conclude that there is no strong ground for discouraging light/moderate alcohol consumption at least in terms of kidney effects [119, 120]. A study from the NHANES III showed that following a healthy lifestyle (BMI, dietary quality, smoking status, and physical activity) was correlated with lower risk of death in adults with non-dialysis CKD [121]. Another study from the Chronic Renal Insufficiency Cohort (CRIC) showed that normal weight (BMI$\leq$25kg/m^2), regular physical activity, and non-smoking were correlated with lower risk of adverse outcomes such as CKD progression, atherosclerotic events and all-cause mortality in individuals with CKD [122].

Lifestyle and behaviors such as smoking and physical activity are intrinsically linked to dietary habits. Patient interventions in this sense prove difficult given the multidimensional aspects of lifestyle to target. The benefits of manipulating multiple components of diet and lifestyle have not been fully assessed.

1.5 DIETARY ASSESSMENT, STUDY DESIGNS: GENERAL CONSIDERATIONS

1.5.1 Dietary Assessment

A number of different methods can assess food intake. Many studies rely on questionnaires called food frequency questionnaires (FFQ). Another way to assess dietary intake is by asking people to recall all the foods (and amounts) they ate over the past 24 hours, which is called 24h dietary recall. Other method for keeping track of food intake is a food diary or food record. People write down and sometime weigh all the food they eat for a week or perhaps even longer. Food diaries have the advantage that they can be quite accurate if done well. The next step is to convert the information from the food questionnaires and food records into nutrient intake, which is done using so-called food composition tables that contain information on the nutrient content of a great variety of foods consumed in a certain region or country. The nutrients include fat, carbohydrate (fiber and sugar), protein, and many vitamins and minerals. Combining the information on how often people eat certain foods with information on the nutrient content of these foods allows researchers to estimate the nutrient intake [123]. One limitation of food composition tables is that they are incomplete: many food products are not listed, which forces nutrition researchers to select an alternative food product to calculate nutrient intake. Further, the amount of added nutrients in the form of additives or preservatives (such as sodium, potassium or phosphorus) in processed foods is not quantified. Nowadays many people use diet and nutrition apps to monitor their food and caloric intake [124]. It is important to note that the described approach to estimate nutrient intake forms the basis of nearly all observational studies. Advantages and disadvantages of dietary assessment methods are listed in **Table 1**.

Table 1 Dietary assessment methods in epidemiological studies [124]

	Methods	Collection date	Advantage	Disadvantage
Food frequency questionnaire	Subjective data collection with predefined, self- or interviewer-administered questions	Habitual intake estimates over a long period	Assessment is simple, cost- and time-effective; good for large cohorts	Specific to study groups and research objectives; a closed-ended questionnaire; low accuracy (recall bias); requires accurate assessment of developed questionnaires
24-Hour dietary recall	Subjective data collection using open-ended templates and assisted by an interviewer	Habitual intake information over the preceding 24 hours	Provides detailed intake information; relatively small respondent burden	Recall bias; trained interviewer required; Interviewer bias; expensive and time-consuming; multiple days required to assess usual intake; possible changes to diet if repeated measures
Dietary record or Dietary diary	Subjective data collection using open-ended, self-administered questionnaires	Actual intake information throughout a specific period; seven days or more	Provides detailed intake data; no interviewer required; no recall bias	Relatively large respondent burden (literacy and high motivation required, possible under-reporting); expensive and time-consuming; multiple days required to assess usual intake; possible changes to diet if repeated measures
Modern techniques	Complementing food frequency questionnaire	Pictures of foods, graphics, etc.	Collects more accurate data	Difficult to convert images into quantitative food intake data; Measurement errors
	Complementing 24-Hour dietary recall	Software, internet, etc.	Standardized data collection (reducing interviewer bias); cost- and time-saving; improves feasibility	Self-report bias
	Complementing dietary records	Software, internet, ipads, mobile phone, application, etc.	Standardized, real-time data collection; cost- and time-saving; improves feasibility	Self-report bias; requires participant training on how to use the technology

1.5.2 Study designs

In this thesis, we have utilized a variety of study designs, each of them with strengths and limitations. **Table 2** provides a quick overview of the various research designs and their strengths and weaknesses in nutrition research.

Table 2 Study design in nutritional epidemiology [125]**.**

Class of study	Type of study	Methods	Timeline	Strength	Limitation
Experimental	Intervention	Randomized control trial	Varies, can be short	Specific factors	Expensive
Observational	Ecological	Population based rather than individual	Existing data	Large number of people and risk-modifying factors	Cannot explore individuals
Observational	Cross-section	Compares existing data for two conditions	Exposure and outcome are assessed at the same time	Many databases are available	Inability to assign temporal relation between exposure and outcome, prone to confounding
Observational	Case-control	Group with disease are collect for the case, disease free subjects for the control	Retrospective	Enable the study of rare disease	Prone to selection bias and confounding
Observational	Cohort-prospective	Assess dietary habits of a large group at the beginning, look at the rate at which they develop disease	Follow up over length of time, years	Most powerful observational study design in epidemiology	Depends on accuracy of food intake reporting

2. AIMS

The overall aim of this thesis was to explore dietary/lifestyle CKD risk factors and implications of kidney dysfunction on dietary-related outcomes.

The specific aims of each study:

To investigate the association between selected single nutrients and CKD outcomes. Studies included:

- Dietary fiber intake and its association with kidney function, inflammation, and mortality risk (**Study I).**
- Serum phosphate levels, as a reflection of dietary phosphorus, and its association with the risk of adverse clinical outcomes in patients with manifest CVD (**Study II).**

To investigate the association between selected dietary patterns and CKD outcomes. Studies included:

- The pro-inflammatory load of the diet as a cause of kidney dysfunction (**Study III).**
- Dietary acid load and the risk of mortality (**Study IV).**

To investigate the association between obesity and incident CKD**.** Study included:

- The possible role of genetic confounding and/or obesity-associated diabetes for the association between obesity and incident CKD (**Study V**).

3. MATERIALS AND METHODS

3.1 PARTICIPANTS

This thesis was developed with data obtained from seven observational cohorts:

3.1.1 ULSAM

The Uppsala Longitudinal Study of Adult Men (ULSAM) is a community survey of all available men born in 1920-24 in Uppsala County, initiated in 1970-1974, when all 50-year-old men living in Uppsala, Sweden, were invited to participate in a health survey. Participants returned for re-examinations at 60, 70, 77 and 82 years of age (http://www2.pubcare.uu.se/ULSAM/). The thesis utilizes the third ULSAM examination cycle, when all participants were 70-71 years old (*n*= 1221, examinations performed during 1991-95) and when 7-day estimated dietary records were collected for the first time. There is information on follow-up characterization of co-morbidity and death.

3.1.2 PIVUS

The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study share a similar design with ULSAM. During 2001-2004, PIVUS invited all 70-year-old individuals (men and women) living in Uppsala, Sweden, to participate in a similar survey with common protocols to ULSAM (http://www.medsci.uu.se/pivus/). PIVUS initially recruited 1016 individuals (507 men and 509 women). Long-term follow up of more than 10 years is available.

3.1.3 SMC

The Swedish Mammography Cohort (SMC) is a population cohort of all women in the Uppsala and Västmanland, Sweden (http://ki.se/en/imm/unit-of-nutritional-epidemiology). All women born in 1914-1948 participated in a mammography screening program were asked to answer a questionnaire about diet and lifestyle in 1987-1990. In late autumn 1997, all women still alive and living in the study area received an expanded questionnaire including 350 diet and lifestyle-related items. A total of 39,227 women (70% response rate) returned this second questionnaire. This thesis was based on the second survey.

3.1.4 COSM

The Swedish Cohort of Men (COSM) is a population cohort of men born in 1918-1952 who at the time of the questionnaire's establishment in 1997 were living in the Västmanland and Örebro. 48,850 (49% response rate) men answered a questionnaire about diet and lifestyle. The questionnaires used and information collected are the same as in the SMC (http://ki.se/en/imm/unit-of-nutritional-epidemiology).

3.1.5 SWEDEHEART

The nationwide Swedish Web-System for Enhancement and Development of Evidence-Based care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry [126] is a National Quality Register that contains patients who are admitted to CCUs or other specialized facilities because of symptoms suggestive of acute coronary syndrome (ACS) in whole Sweden. The registry prospectively collects information on patient demographics, cardiovascular

risk factors, medical histories, and in-hospital treatments such as coronary revascularization procedures, hospital outcomes, discharge medications, and diagnoses. Included until 2015 are more than 800.000 incident cases.

3.1.6 SCREAM

The Stockholm CREAtinine Measurements (SCREAM) project is a healthcare data register of all Stockholm citizens accessing healthcare and having a creatinine test taken (about 1.3 million individuals) during 2006-2011 [127]. Given the commonness of creatinine testing, SCREAM captures a large proportion of the complete population census, making it valid for public health research, estimation of disease burden and projections. We performed a linkage between the national SWEDEHEART and regional SCREAM, identifying approximately 28.000 Stockholm residents with ACS with complete laboratory data during follow up.

3.1.7 The Swedish Twin Registry

The Swedish Twin Registry (STR) is a Swedish population-based cohort initiated in late 1950s; obtains information on twin births occurring in Sweden from National Board of Health and Welfare; contains more than 194,000 twins and more than 75,000 pairs today [128]. Twins born before 1958 were contacted for the first time interview during the Screening Across Lifespan Twin (SALT) study from STR, with the purpose of screening all twins in Sweden for common complex diseases, including about 44,825 twins. Questionnaires that included questions about illness and health, medication use, occupation, education and life style factors were conducted during 1998-2002 [129].

3.2 STUDY DESIGNS

Because of specific exclusion criteria in each study and at times missing values of study exposure or outcomes, the number of individuals and main parameters considered in each of the studies vary, being summarized in **Table 3.**

Table 3. Description for each study

Study	Cohort	Subjects	Exposure	Outcome
I	ULSAM	1,110	Dietary fiber	Kidney function, inflammation, and mortality
II	Linkage between SWEDEHEART and SCREAM	2,547	Serum phosphate	In-hospital death and events; 1 year post-discharge CVD events and mortality
III	ULSAM and PIVUS	1,942	Pro-inflammatory diet pattern	Inflammation and kidney function
IV	COSM and SMC	81,427	Dietary acid load	CVD mortality and all-cause mortality
V	SALT	29,136	BMI	CKD incidence; diabetes incidence

Abbreviation: COSM, Swedish Cohort of Men; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; SALT, Screening Across Lifespan Twin study; SCREAM, Stockholm CREAtinine Measurements project; SMC, Swedish Mammography Cohort ; SWEDEHEART, Swedish Web-System for Enhancement and Development of Evidence-Based care in Heart Disease Evaluated According to Recommended Therapies registry; ULSAM, Uppsala Longitudinal Study of Adult Men.

3.2.1 Study I

This is an observational cohort study using data from the ULSAM. Exclusion criteria were lack of data on 7-day dietary records and/or serum cystatin C (n=116), and extreme values of reported energy intake (<765 or >4300 kcal/day; n=5). Study I therefore comprised 1110 participants.

3.2.2 Study II

This is an observational cohort study linking SWEDEHEART and SCREAM through the personal identification number of each citizen. We included all patient undergoing at least one serum phosphate measurement within 24-hours before hospital admission and the discharge date. There were 2,547 patients (1,743 men and 804 women, mean age 67±14 years) identified and constitute the study population.

3.2.3 Study III

This is a cross-sectional study including individuals from two community-based cohorts: the ULSAM and PIVUS. Exclusion in ULSAM was unavailable data on dietary records, missing serum cystatin C or creatinine, and extreme values of reported energy intake (<765 or >4300 kcal/day), leaving 1,097 ULSAM participants for this analysis. Exclusion in PIVUS was unavailable data on dietary records, serum cystatin C or creatinine, and extreme values of energy intake, leaving 845 (422 of which women) PIVUS participants for this analysis. Altogether, the joint population for study III included 1,942 (22% women) individuals.

3.2.4 Study IV

This is an observational cohort study including individuals from two community-based cohorts: the COSM and SMC. We excluded subjects with missing personal identification number, died before the start of follow up, those with baseline history of cancer, those with a history/diagnosis of CKD, and those with implausible energy intake. A total of 81,427 individuals (36,470 women and 44,957 men) were finally included in Study IV.

3.2.5 Study V

This is an observational cohort study including self-reported weight and height to estimate BMI from the Swedish Twin Registry. We excluded participants with missing information on birth date, if his/her twin did not report weight or height, or if information of zygosity was missing. Finally, we excluded participants with history of CKD and diabetes. A total 29,136 twins (14,568 twin pairs) were eligible for inclusion in **Study V**, comprising 10,600 opposite-sex fraternal twins, 10,694 same-sex fraternal twins and 7,842 identical twins.

3.3 METHODS

3.3.1 Dietary assessments

In ULSAM and PIVUS, dietary nutrients were evaluated by 7-day dietary records using a pre-coded menu-book, previously designed and validated by the Swedish National Food Administration (NFA) [130]. The participants were given oral instructions by a dietitian on how to perform the dietary registration. The daily intake of energy and daily intake of macro-and micro-nutrients were thereafter calculated by use of a computerized program based on food composition tables from the Swedish NFA.

In COSM and SMC, dietary intake was assessed with a 96-item food frequency questionnaire (FFQ). Participants reported how often, on average, they had consumed selected foods over the previous year by using predefined frequencies of consumption[131].

The daily intake of macro-and micro-nutrients in the thesis were corrected for total energy intake through the regression analysis of the residual method [132].

3.3.2 Laboratory analyses

In ULSAM and PIVUS, the assays were performed at the Department of Clinical Chemistry, University Hospital, Uppsala, with detailed methods specified in the papers of this thesis. In the linkage between SWEDEHEART and SCREAM, laboratory measurements were performed during the patient's CCUs admission and by the clinical laboratories providing services to Stockholm County Council.

3.3.3 Follow up

Complete follow-up of the cohorts were obtained through record linkages to the Swedish In-Patient Register, the Death (National Board of Health and Welfare), Population Register and the Swedish Renal Register (SNR) (http://www.medscinet.net/snr/).

3.3.4 Statistical analyses

All analyses were performed using Stata version 15.0 (StataCorp, College Station, TX) and R (https://www.r-project.org).

For cohort analyses, we used the traditional Cox proportional hazards model in **Study I, II, IV and V**. In addition, we investigated "dose-response" relationships between exposure and outcomes using flexible splines curve in **Study II, IV and V** [133]. Interaction terms in *specific* strata were also tested in **Study I, II, IV and V.** We also performed Fine-Gray models accounting for death due to non-CVD causes as a competing event in **Study II**.

Study III used the multiple-mediation analysis [134, 135] to address the pro-inflammatory load of the diet as a cause of kidney dysfunction and whether effect of diet on inflammation explained this association.

Study V performed a co-twin control analysis using stratified Cox regression models (clustering the twins in pairs) in order to control for shared factors between the twins, such as age, sex, genes and environment shared prior to the study. We also considered incident diabetes as a time-dependent covariate/mediator in the models. The weighted contribution of overweight and obesity to the risk of CKD was quantified with the population attributable fraction [136] .

4. MAIN RESULTS AND DISCUSSION

4.1 FIBER, KIDNEY FUNCTION, INFLAMMATION AND MORTALITY

In **study I**, we showed that dietary fiber positively correlated with eGFR regardless of multiple confounders (**Table 4**). The finding is in agreement with several small sample size studies that described a relationship between dietary fiber intake, decreased blood urea nitrogen and increased fecal nitrogen excretion in CKD patients [137-139]. We also showed that dietary fiber negatively correlated (albeit weakly) with inflammation surrogates.

Table 4. Association of fiber intake with estimated glomerular filtration rate (mL/min/1.73m^2).

		Unadjusted		Adjusted	
	Cut point/limits	Difference (95% CI)	*P* value	Difference (95% CI)	*P* value
Continuous Model	10g/day higher	3.7 (1.6, 5.9)	0.001	2.6 (0.3, 4.9)	0.03
Multi-category Model					
Quartile 1	≤14.5 g/day	Reference		Reference	
Quartile 2	>14.5-16.8 g/day	1.4(-0.9,3.7)	0.24	1.5 (-1.0,4.0)	0.23
Quartile 3	>16.8-19.2 g/day	2.3(0.1,4.6)	0.05	1.4 (-1.1,3.9)	0.27
Quartile 4	> 19.2 g/day	4.2(1.9,6.5)	<0.001	2.9 (0.5,5.4)	0.02
P for trend		0.01		0.08	

Model adjusted for protein intake, age, BMI, smoking, physical activity, education, comorbidities (cardiovascular disease, diabetes, hyperlipidemia, and hypertension), and urinary albumin excretion rate. Modified from [39].

We observed that lower fiber intake was more strongly associated with mortality in individuals with CKD than in those without; this association was independent of calorie and protein intake, lifestyle factors, as well as co-morbidities. Our results expanded previous observations from the U.S. [38]. However, contrary to our initial hypothesis, we did not observe any correlation between dietary fiber and CVD-related mortality. Instead, the association between fiber and survival was mainly explained by lower risk of cancer-related mortality. Finally, we observed a significant interaction product term between dietary fiber and eGFR in predicting both all-cause and cancer-mortality. **Figure 1** showed that after stratification, dietary fiber intake was associated with all-cause and cancer related death in individuals with CKD. We observed no association in those without CKD.

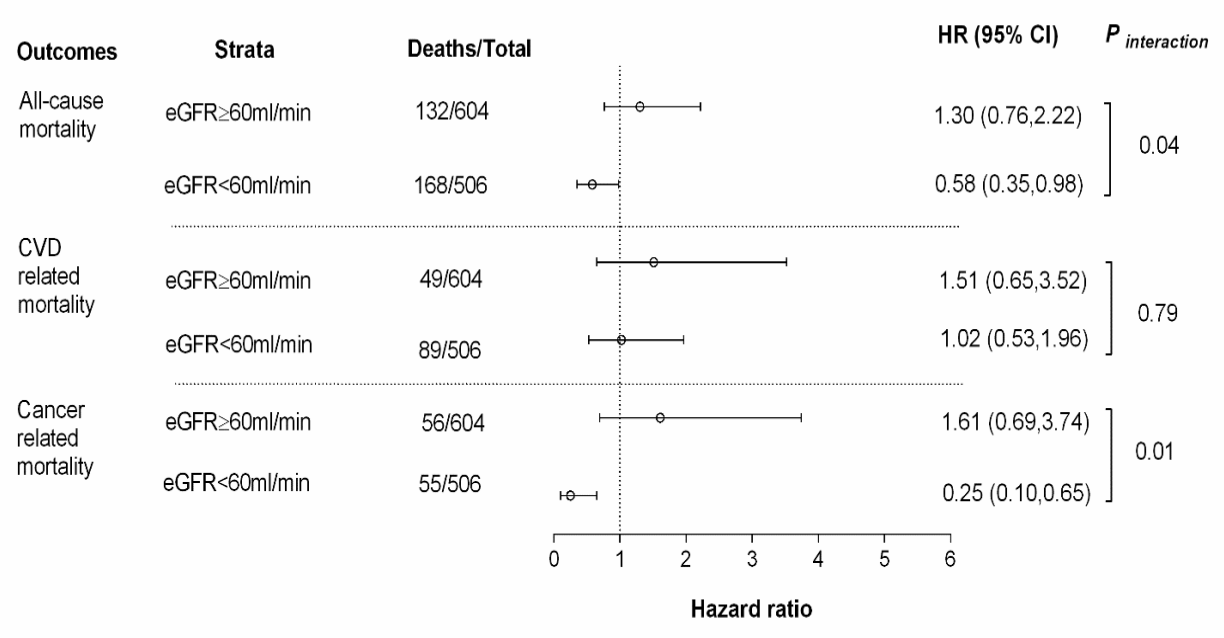

Figure 1. Hazard ratios and 95% confidence intervals for dietary fiber (per 10g/day higher) with all-cause, CVD and cancer related mortality, stratified by the presence/absence of kidney dysfunction in the entire survey. Reprinted with permission [39].

4.2 SERUM PHOSPHATE AND ADVERSE OUTCOMES

Study II showed a J-shaped association between serum phosphate levels and the risk of in-hospital adverse events and mortality (**Figure 2**). In patients with higher phosphate concentrations, the risk of CVD event was higher but somewhat flattened (**Figure 2B**). Low phosphate levels probably reflect malnutrition, vitamin D deficiency and/or primary hyperparathyroidism, mechanisms that may lie behind this association [140].

One advantage of our analyses with regards to previous studies [141-143] is the use of models that allow for non-linear associations, and models that consider the competing risk of death for other causes [144]. In summary **Study II** showed that both higher and lower phosphate levels associated with increased risk of adverse outcomes during the index hospitalization and within one- year post-discharge in patients with suspected ACS. Risk associations were already present in the normal-range of serum phosphate levels.

A) B)

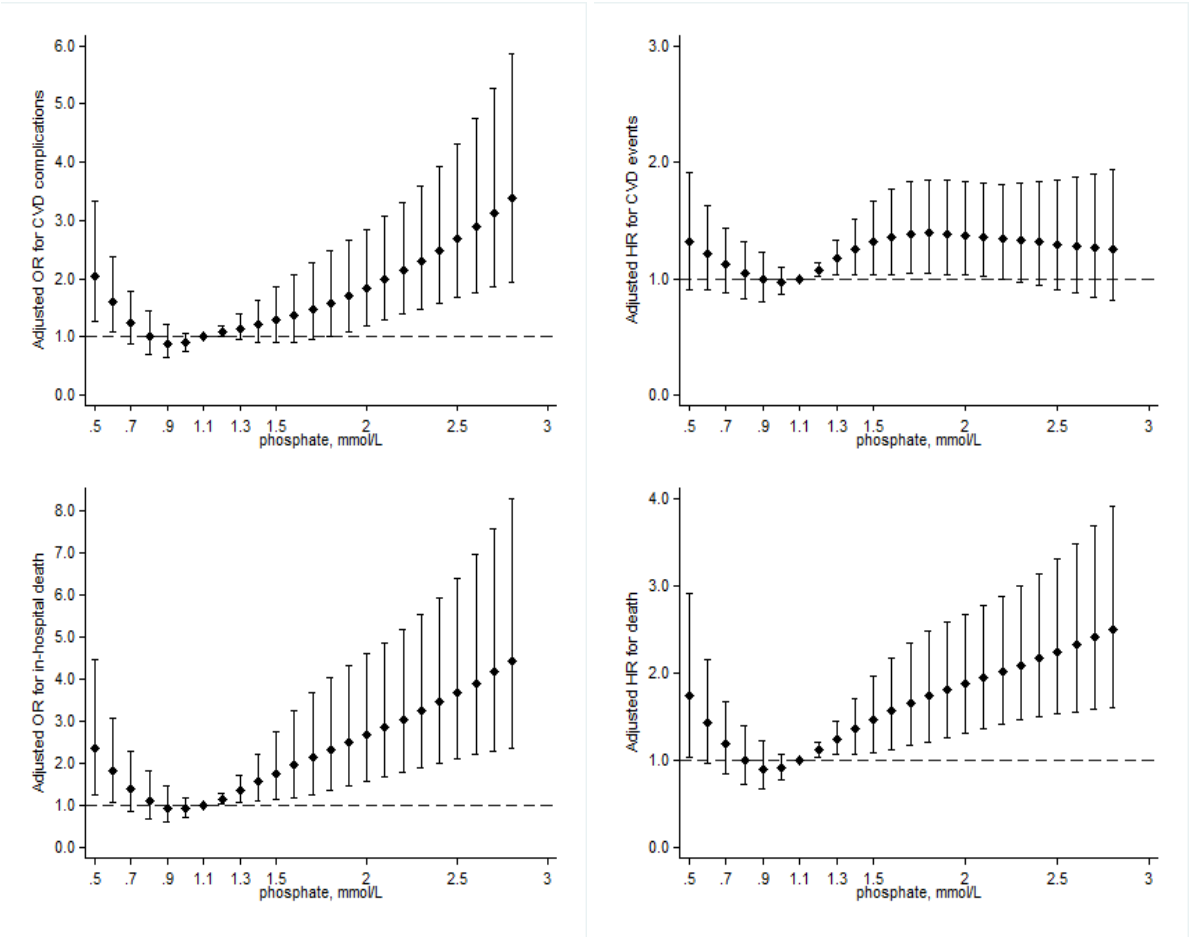

Figure 2. A) Odd ratios and 95% confidence intervals for the composite of in-hospital CVD complications or in-hospital death associated with serum phosphate (mmol/L). **B)** Hazard ratios and 95% confidence intervals for the 1-year composite of CVD events and death associated with serum phosphate (mmol/L) in patients discharged alive. Reprinted with permission [60].

4.3 INFLAMMATORY DIET AND KIDNEY FUNCTION

Study III combined pro-inflammatory and anti-inflammatory effects of nutrients, vitamins, and trace elements, generated a dietary pattern, and correlated it with both renal function and inflammation (**Table 5**). Our study also suggested that the association between this dietary pattern and kidney function was partly explained by systemic inflammation.

Table 5. Associations between adapted dietary inflammatory index (ADII) and serum CRP levels, and between CRP levels and estimated kidney function, among 1942 elderly adults aged 70-71 years.

	β coefficients (95% CI)			
	Crude	p	Adjusted Model	p
Association between ADII (per SD increase of 3.26) and CRP levels				
CRP, mg/L	0.06 (0.02, 0.11)	0.01	0.06 (0.01, 0.10)	0.01
Association between CRP levels (per mg/L1 increase) and eGFR				
eGFR CKD-EPIcys, mL/(min.1.73 m2)	-0.06 (-0.07, -0.04)	<0.001	-0.05 (-0.06, -0.04)	<0.001
eGFR CKD-EPI cys+crea, mL/(min.1.73 m2)	-0.04 (-0.05, -0.03)	<0.001	-0.04 (-0.04, -0.03)	<0.001

Model adjusted for energy intake, age, sex, BMI, smoking status, physical activity, hypertension, diabetes, lipid-lowering medication and cohort (ULSAM or PIVUS). Abbreviations: ADII, adapted dietary inflammatory index; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate. Reprinted with permission [103].

4.4 DIETARY ACID LOAD AND MORTALITY

Study IV showed a dose-response correlation between acid load and mortality. Mortality rates in PRAL extreme values was higher, showing an approximately U-shaped relationship. High PRAL (increased dietary acidity) and low PRAL (increased dietary alkalinity) were associated with all-cause and CVD related death. In general, the magnitude of this association was small (**Figure 3**).

Previous studies have identified pathways association with PRAL and CVD risk perhaps because of the use of statistical analyses that assume relationships to be linear, something that not often occurs in biology. We concluded that an acid-base balanced diet was associated with the lowest mortality risk, but the magnitude of this mortality reduction was modest.

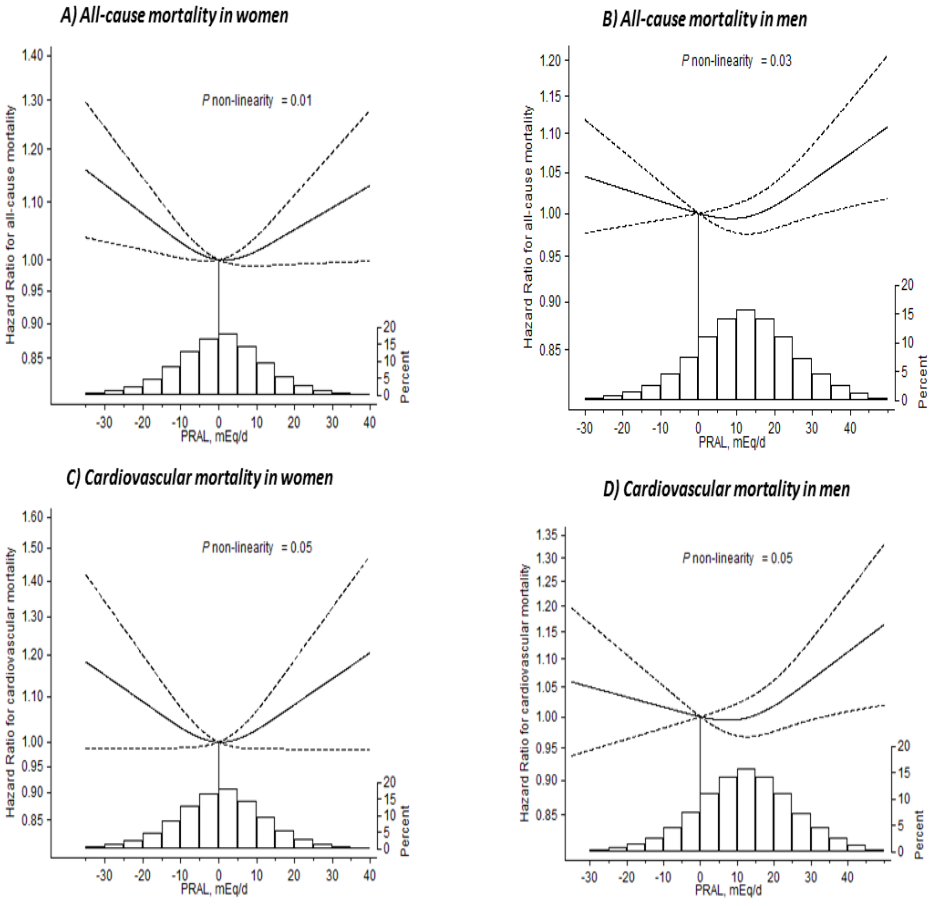

Figure 3. Hazard ratios and 95% confidence intervals for all-cause in A) women and B) men and cardiovascular mortality in C) women and D) men associated with PRAL (mEq/day). Reprinted with permission [90].

4.5 BMI AND CKD

We observed that controlling for shared risk factors between twin pairs minimally affected the association between BMI and CKD **(Table 6)**. This was true for both fraternal and identical twins. In twins with discordant BMI, heavier siblings had a higher adjusted incidence rate of CKD than leaner ones, particularly when BMI differed >2 kg/m^2. Regardless of baseline BMI, heavier siblings presented a higher CKD risk than leaner ones, findings altogether that are congruent with a direct effect.

In Table 7, after adjusting for diabetes development, the strength of the association was reduced (suggesting effect mediation), but remained clinically and statistically significant. Thus, our findings provide strong evidence of a direct effect between a high BMI and subsequent CKD risk. Our population attributable fraction analysis showed that a large proportion of CKD cases may be prevented if the population maintained a normal BMI**.**

We conclude that a higher BMI, irrespective of genetic confounding or incident diabetes, is associated with CKD and congruent with a direct effect.

Table 6. Cohort and Co-twin control analyses: Hazard Ratio of incident CKD during follow up.

BMI, (per kg/m^2)	Person-Years	Cases	HR	95% CI
Incident CKD				
Cohort analysis (n=29,136)	381,434	1,113	1.13***	1.11,1.14
Co-twin controlled analyses				
Fraternal Twins (opposite sex, n=10,600)	138,129	435	1.18***	1.12,1.26
Fraternal Twins (same sex, n=10,694)	140,091	387	1.16***	1.09,1.22
Identical twins (n=7,842)	103,214	291	1.17**	1.06,1.29
P for interaction			0.18	

HR adjusted for age, sex, comorbidities (CVD, hypertension and cancer history) and life style habits (alcohol abuse, attained education and smoking). Multiplicative interaction between zygosity type and BMI.

Table 7. Cohort and Co-twin control analyses: Hazard Ratio of incident CKD adjusted for the occurrence of diabetes mellitus during follow up.

BMI, per kg/m^2 increase	HR	95% CI
Cohort analyses		
Adjusted model	1.13***	1.11,1.14
Further adjustment for incident DM (time-varying covariate)	1.06***	1.04,1.08
Co-twin controlled analyses		
Fraternal Twins (opposite sex)		
Adjusted model	1.18***	1.12,1.26
Further adjustment for incident DM (time-varying covariate)	1.12**	1.05,1.20
Fraternal Twins (same sex)		
Adjusted model	1.16***	1.09,1.22
Further adjustment for incident DM (time-varying covariate)	1.10**	1.04,1.17
Identical Twins		
Adjusted model	1.17**	1.06,1.29
Further adjustment for incident DM (time-varying covariate)	1.12*	1.01,1.25

Model adjusted for age, sex, comorbidities (CVD, hypertension and cancer history) and life style habits (alcohol abuse, attained education and smoking). p<0.05, **p<0.01, ***p<0.001.

4.6 STUDY CONSIDERATIONS

4.6.1 Strengths of the studies

Strengths of this thesis include the population-based cohort study designs, detailed data on food/nutrients/lifestyle, rich information of confounders, and prospective follow up collection via register linkage, with virtually no losses to follow-up. In some cohorts, participants had the same age, sex and geographical original. In others, the study population contained participants from a defined area where all citizens received universal and tax-funded health care. The twin cohort is an invaluable study design to control for genetic confounding [145] and to detect the extent to which an association between the environment and an outcome variable is due to familial confounding.

4.6.2 Limitations of the studies

Selection bias

The voluntary screening nature of some of the cohorts here presented in this thesis may introduce selection bias, as individuals in good health and interested in diet/lifestyle may be more prone to participate. Conversely, non-responders may have poorer health and higher co-morbidity burden (**Study I, III, IV, V)**. In **Study I and II**, the inclusion of Swedish Caucasian individuals of 70-71 years old is a strength in the sense that minimizes the impact of aging in these associations, but it also limits the generalizability of our results to be generally applicable to other races or younger peoples (**Study I, III**). Finally, we included patients with hospitals suspected having ACS who had an indication for phosphate testing (**Study II)**, so they may not be extrapolated to the general ACS population.

Confounding and reverse causation bias

Confounding is an inherent characteristic of all observational studies. We have tried to take this into account by adjusting for known ones, but not for residual, unmeasured and unknown confounding. Further, errors during participants' completion of food records (recall bias), risks of over-reporting in lean people or underreporting in obese ones [124] may introduce further bias.

The studies in the thesis aimed to understand the effect of diet/lifestyle on CKD outcomes, which implies a direction of causation. Assessing causality in observational studies is not possible and associations could operate in both directions. This is often referred to as reverse causation bias: e.g. that lower fiber intake is not a risk factor but instead a consequence of dietary adaptions in CKD (S**tudy I)**. We attempted several statistical approaches to tackle this in **Study III**, including mediation analysis. In **Studies I, IV and V**, we performed sensitivity analyses excluding selected participants or immediate person time of follow up.

Misclassification Bias

Regarding exposure

Not all possible foods are contemplated in the food frequency questionnaires/records, which limits our capacity to accurately account for everything eaten. For instance, in some of our cohorts there was no information in the intake of food supplements. This unavoidable limitation of dietary

assessments can lead to exposure misclassification, something that in this thesis we have assumed to be non-differential. We generally lack biomarkers in plasma/serum or urine to validate our diet findings and base our assumptions that intake of nutrients lead to modification of plasma/serum biomarkers on previous interventional evidence [146].

In **Study V**, BMI was self-reported and BMI itself is a rough measure of adiposity (e.g. models only body weight, and a muscular person would also appear as obese). Although other more reliable measures such as waist circumference or body fat composition would have been preferred, this may be a lesser problem in large population-based samples.

Regarding outcomes

Many of study outcomes are based on diagnoses in healthcare, which may be affected by detection bias if healthcare is not sought. For instance, the outcome in **Study V** was CKD diagnosis. However, given the unique nature of participants (twins), we assumed that diagnosis of chronic diseases in a sibling would prompt similar investigations and follow up in the other one. We considered one eGFR estimate as our outcome in **Study III**, which is subjected to measurement variability and would not comply with current recommendations to define CKD on the basis of two consecutive reduced eGFR measurements. However, on the other hand, imposing two consecutive healthcare visits to define this rare outcome may overemphasize sicker individuals accessing healthcare more frequently.

5. CONCLUSIONS

This thesis reports associations of various dietary and lifestyle factors with the risk of kidney disease and other related outcomes. The main conclusions are:

1. A higher dietary fiber intake is associated with better kidney function and lower inflammation in community-dwelling men. A high fiber intake is also associated with lower mortality risk, especially in individuals with manifest CKD.

2. In men and women with suspected acute coronary syndrome, both higher and lower phosphate levels associate with increased risk of adverse outcomes during the index hospitalization and within one year post-discharge. The risk association is however present already within normal-range serum phosphate values.

3. A pro-inflammatory dietary pattern correlates with both kidney function and systemic inflammatory biomarkers in community-dwelling elderly men and women. In addition, the association between this dietary pattern and kidney function is explained by systemic inflammation.

4. Excess diet alkalinity and acidity, both show weak associations with mortality in a U-shape fashion in population screenings of men and women. An acid-base balanced diet is associated with the lowest mortality, but the magnitude of mortality reduction is modest and dietary modifications of diet's alkalinity may not be very relevant overall to reduce mortality risk.

5. A higher BMI, irrespective of genetic confounding or incident diabetes, is associated with CKD among twins.

6. FUTURE PERSPECTIVES

Results from this thesis provide pieces of evidence that improve our understanding of the large and complex puzzle of the relationships between diet, lifestyle and chronic kidney disease. Overall, our results support the premise that healthy dietary/lifestyle modifications may represent relevant strategies to improve kidney health and clinical outcomes.

The high incidence of CKD is a major public health concern. While this thesis focused on the impact of some selected single nutrients, and dietary pattern and lifestyles, many other factors remain poorly studied. I would like to continue exploring these topics and evaluate, for instance, aspects of nutrient quality in CKD management. This may involve the effects of plant vs animal protein, organic vs inorganic phosphorus, and improved quality of the intake of dietary fat, carbohydrates and protein.

Our studies, and previous literature, define CKD on the bases of a reduced estimated GFR. Although this is a currently accepted definition, it may lead to an overrepresentation of the effects exerted by ageing among the elderly. Many clinicians would consider a low kidney function among elderly individuals to be normal for their age. Separating age-related kidney function decline from disease-related kidney function decline is at present not easy. Future studies should attempt to better separate lifestyle risks factors for CKD in the community (primary prevention) from those to retard disease in nephrology-referred patients (secondary prevention).

For life style factors, our findings may have implications for public health programs aiming at improving clinical outcomes. The large population-based Swedish twin registry offered a unique opportunity to assess the impact of lifestyle on CKD outcomes. An interpretation of our results is that a combination of environmental and lifestyle factors are likely responsible for an increased CKD risk attributed to obesity, and this information could have direct application into public health prevention campaigns. Although genetic factors can predispose to aggravate the consequences of an unhealthy lifestyle, environmental factors can substantially modify genetics-related risks. The results support the hypothesis that interventions performed to promote weight loss will be effective in reducing the risk of CKD. Other lifestyle factors, such as alcohol consumption, smoking and physical activity are other factors of interest to study in the future.

Considering the commonness of CKD in the general population, more studies supporting the role that specific dietary patterns may exert on its onset can have an impact on public health policies, while establish the ground for dedicated holistic dietary interventions in this population. Efficient trial designs, perhaps linked to registries (registry-randomized trial) or to electronic health records may increase the trial feasibility and reduce costs. Considering the unique dietary needs of persons with CKD, these trials are necessary to inform clinical decisions and patient recommendations. I understand that nutritional trials requires a lot of resources and time, as well as many challenges on how to ensure dietary compliance or change unhealthy habits. Success probably requires the integrated effort of nephrologists, dietitians, physiotherapists, endocrinologists and nurses.

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